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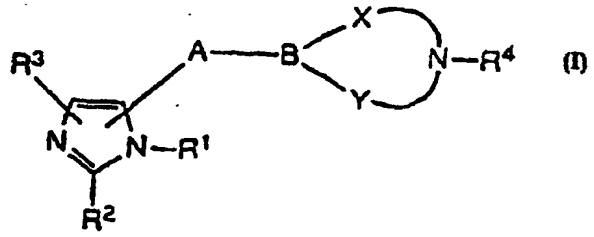

(I)

(57) Abstract

The invention relates to new imidazole derivatives of formula (I) having agonistic and antagonistic activity on the histamine H_3-receptor. More in particular the invention concerns 4- and 5-substituted aminoalkyl imidazoles and their derivatives. The invention further relates to the synthesis of these compounds, pharmaceutical compositions comprising the said compounds or pharmacological salts thereof, and the use of the compounds as agents having biological activity on the histamine H_3-receptor or for the preparation of a pharmaceutical composition.

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NEW IMIDAZOLE DERIVATIVES HAVING AGONISTIC OR ANTAGONISTIC ACTIVITY ON THE HISTAMINE H_3 RECEPTOR.

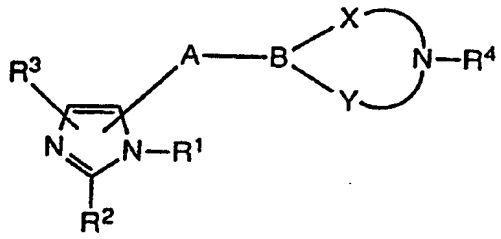
The invention relates to novel imidazole derivatives having pharmacological activity. The invention is in particular directed to novel imidazole derivatives having agonistic or antagonistic activity on the histamine H_3 receptor. More in particular the invention concerns 4- and 5-substituted aminoalkyl imidazoles and their derivatives.

The invention further relates to the synthesis of such compounds, pharmaceutical compositions comprising such compounds or pharmacological acceptable salts thereof, and the use of the compounds as agents having biological activity, as agents with agonistic or antagonistic activity on the histamine H_3 receptor or for preparing a pharmaceutical composition.

The histamine H_3 receptor is a presynaptic receptor, located in both the central and peripheral nervous system, the skin and in several organs such as the lung, the intestine and probably also in the spleen and the gastro-intestinal tract. Stimulation of the H_3 receptor leads to inhibition of the release of histamine (autoreceptor), but also of other neurotransmitters (heteroreceptor), such as e.g. acetylcholine and serotonine.

A number of selective H_3 ligands have been described. For a review see Leurs et al., Progress in Drug Res. 39, p. 127-165 (1992) and Lipp et al., in The Histamine Receptor, Wiley-Liss, Inc., p. 57-72 (1992). It has been shown that the H_3 receptor can be regarded as a general regulatory system and as a potential target for new therapeutics (Timmerman, J. Med. Chem. 33, p. 4-11 (1990) and Schwartz et al., Agents and Actions 30, 1/2, p. 13-23 (1990)).

Now a group of new imidazole derivatives showing agonistic or antagonistic activity on the H_3 receptor has been identified. These derivatives can be represented by the general formula:

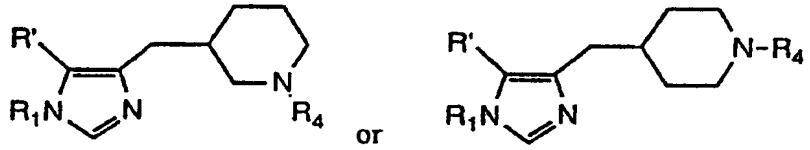


(I)

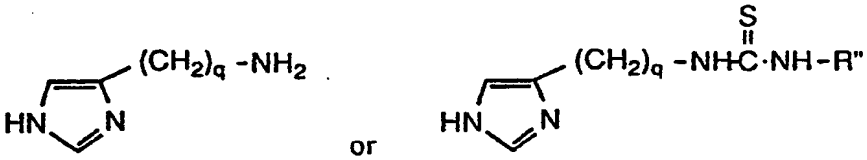
wherein the substituents are as defined in claim 1.

The imidazole derivatives of the present invention show either antagonistic or agonistic activity on the histamine H_3-receptor and may therefore be used as the active ingredient of pharmaceutical compositions.

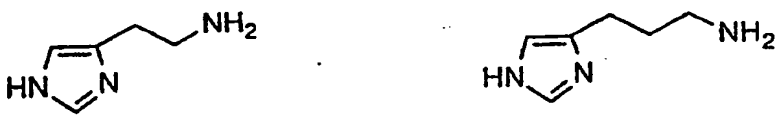
The compounds of the formulas

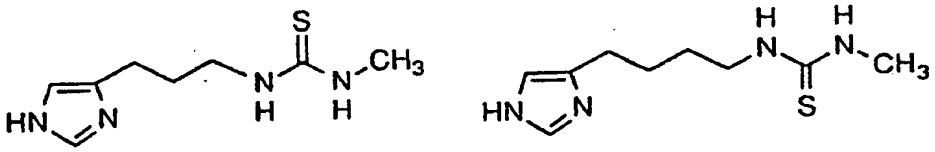


wherein R' is hydrogen, methyl or ethyl and compounds of the formulas

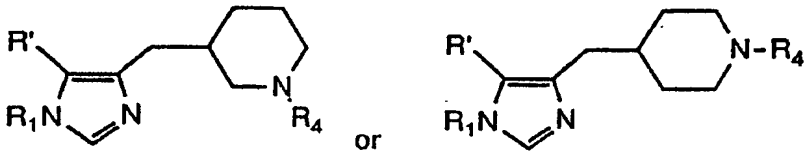


wherein q is 2-5 and R" is hydrogen, (C_1-C_3)alkyl, aryl or aryl-(C_1-C_3)alkyl have been previously disclosed. Of these compounds only derivatives of the formulas





and compounds of the formulas

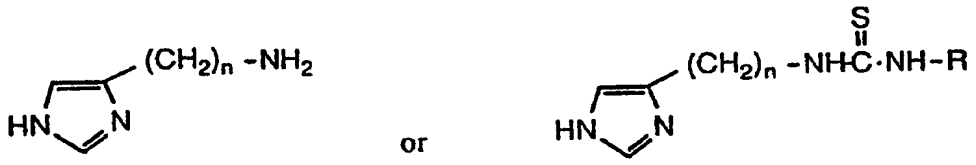


wherein R' is hydrogen, methyl, ethyl.

are known to have (ant)agonistic activity on the H_3-receptor.

The present invention comprises both linear and ringstructured compounds, all of which have the imidazole-part in common.

The linear compounds have for example one of the formulas



(II) (III)

Compounds of formula I may be synthesized in general through a process that is analogous to the process as described in Vollinga et al., Recl. Trav. Chim. Pays-Bas, 112, p. 123-125 (1993). The process preferably comprises C5-lithiation of a 1,2-diprotected imidazole and subsequent treatment with a suitable electrophile. The electrophile may be selected from the group consisting of halogen, aldehyde, keton, nitrile, epoxide or acylhalide.

In general compounds of formula I (compounds with R^4 is hydrogen excluded) can be prepared from compounds of formula I wherein R^4 represents hydrogen. For example compounds of formula III can be made from the compounds of formula II by simple addition or condensation reactions e.g. VUF 4613 can be made by the addition of methylisothiocyanate to VUF 4702.

For the synthesis of compounds of formula II, 1-chloro-ω-iodoalkanes can be used as electrophiles. In this

matter, an ω-chloroalkane is introduced on the C5-position of the 1,2-diprotected imidazole. The chloro group can then be converted into an amino group and the protection groups removed.

Other compounds of formula I (excluding the compounds of formula II and III) have been made using aldehydes or ketones as electrophiles with subsequent removal, conversion or elimination of the formed hydroxyl group.

Of the imidazole derivatives of the invention VUF 4702 (4(5)-(5-aminopentyl)-1 H-imidazole dioxalate) shows a particular advantageous antagonistic activity, whereas VUF 4708 (4-[(4(5)-imidazolyl)methyl]piperidine) is a good agonist.

The following examples illustrate the synthesis of compounds of the present invention, but are never intended to limit the scope thereof.

EXAMPLE 1

Synthesis of 4(5)-(5-aminopentyl)-imidazole dioxalate (VUF 4702).

100 gram imidazole (1.5 mol), 160 ml dimethylsulfamoylchloride (1.5 mol) and 210 ml triethylamine (1.5 mol) were dissolved in 1000 ml toluene. After 16 hours of stirring, the precipitate was filtrated and the filtrate was concentrated under vacuo. The product (1-(N,N-dimethyl-sulfamoyl)imidazole) was distilled. Boiling point : 110°C at 0.4 mm Hg.

17.5 g. of 1-(N,N-Dimethylsulfamoyl)imidazole (0.1 mol) was dissolved in dry THF (400 ml) under an atmosphere of dry nitrogen and cooled to -70°C. n-Butyllithium in hexane (65 ml, 0.1 mol) was added dropwise (temperature should not exceed -65°C). After 15 min, a solution of tert-butyl-dimethylsilyl chloride (15 g, 0.1 mol) in dry THF (30 ml) was added (10 min) and the solution was stirred at room temperature for 1 h. The mixture was cooled to -70°C again and n-butyllithium in hexane (65 ml, 0.1 mol) was added dropwise (temperature should not exceed -65°C). After

0.5 h, a solution of 1-chloro-5-iodopentane (23.3 g, 0.1 mol) in dry THF (20 ml) was added gradually and the mixture was allowed to (slowly) warm to room temperature overnight. The reaction mixture was poured into water (200 ml) and the THF was removed under reduced pressure. The product was extracted with $CHCl_3$ (3 x 150 ml), dried (Na_2SO_4) and concentrated in vacuo.

The residue and phthalimide (15.0 g, mol) were dissolved in DMF (300 ml), Na_2CO_3 was added (12.0 g, mol) and the mixture was heated at 90°C. After 7 h the mixture was filtrated and the solvent was evaporated under reduced pressure. The residue was dissolved in $CHCl_3$ (150 ml), washed with H_2O (3 x 150 ml), dried (Na_2SO_4) and concentrated in vacuo.

The crude product was dissolved in 30 % HBr (300 ml) and heated under reflux. After 16 h the mixture was cooled, filtrated and concentrated under vacuo. The residue was dissolved in absolute EtOH (300 ml), heated under reflux for 0.5 h and concentrated under reduced pressure. The remaining dark oil was washed (under stirring) with portions (100 ml) of acetone. After several washings, the oil crystallized. The residue was dissolved in H_2O and the pH was raised to 12 by adding K_2CO_3. The product was extracted with $CDCl_3$, dried on Na_2SO_4 and concentrated under vacuo. The product was dissolved in iso-propanol and an excess of a saturated solution of oxalic acid in iso-propanol was added (slowly). The formed precipitate was collected by centrifugation and washed with iso-propanol (three times). After recrystalization from methanol/iso-propanol, VUF 4702 was obtained as white crystals. The melting point was 155.7-156.6°C.

EXAMPLE 2

Synthesis of 4(5)-(-aminoalkyl)imidazole-derivatives.

Analogous to the preparation method of VUF 4702 from example 1, a number of compounds were synthesized according to formula II, using the corresponding 1-chloro-ω

-iodoalkane. The meaning of n, the melting points and the exact mass results are given in the table below.

compound	n	melt. point (°C)	salt	ex. mass (measured)	ex. mass (calculated)
VUF 4701	4	129.0-134.0	di HBr	139.1112	139.1109
VUF 4702	5	155.7-156.6	diox.	153.1266	153.1266
VUF 4732	6	132.0	diox.		
VUF 4733	8	95-100	diox.		
VUF 4734	10	154.5-155.0	diox.		

EXAMPLE 3

Synthesis of N-methyl-N'-[6-(4(5)-imidazolyl)hexyl]thiourea oxalate (VUF 4740)

3 mmol VUF 4732 as dihydrobromic acid, was added to a solution of 6 mmol sodium dissolved in absolute ethanol. This solution was refluxed for one half hour, and the formed precipitate (after cooling to roomtemperature) was filtrated.

9.0 mmol methylisothiocyanate was added to the filtrate. After refluxing the reaction mixture for 2 hours, the ethanol was evaporated and the product was purified on a column packed with flash-silicagel with first ethylacetate as eluent (product stays on column : R_f = 0-0.1; methylisothiocyanate eluted R_f = 1.0). The product was subsequently eluted with methanol as eluent (R_f = 1.0). The product was dissolved in ethylacetate and an excess of a saturated solution of oxalic acid in ethylacetate was added (slowly). The formed precipitate was collected by centrifugation and washed with ethylacetate (three times). After recrystalization from absolute ethanol, VUF 4740 was obtained as white crystals. The melting point was 106.5-110.0°C.

EXAMPLE 4

Synthesis of N-substituted-N'-[ω-(4(5)-imidazolyl)alkyl]-thiourea-derivatives.

Analogous to the preparation method of VUF 4740 from example 3, a number of compounds were synthesized according to formula III, using the corresponding 4(5)-(ω-aminoalkyl)-imidazole-derivative. The meaning of n, the melting points and the exact mass results are given in the table below.

compound	n	R	melt. point (°C)	salt	ex. mass (measured)	ex.mass (calculated)
VUF 4577	2	methyl	99.9-100.8	HBr	184.0782	184.0783
VUF 4578	2	ethyl	164.5-165.0	HBr	198.0940	198.0939
VUF 4579	2	n-propyl	172.6-173.1	HBr	212.1100	212.1096
VUF 4580	2	i-propyl	123.1	ox	212.1090	212.1096
VUF 4581	2	cyclohexyl	161.7	ox	252.1401	252.1409
VUF 4582	2	phenyl	148.6-148.9	HBr	246.0931	246.0939
VUF 4583	2	benzyl	153.7-155.0	ox	260.1101	260.1096
VUF 4584	2	phenylethyl	145.1-145.5	ox	274.1253	274.1252
VUF 4631	3	ethyl	116.1	ox	212.1092	212.1096
VUF 4632	3	n-propyl	123.2-125.2	ox	226.1265	226.1252
VUF 4633	3	i-propyl	146.0	ox	226.1271	226.1252
VUF 4634	3	cyclohexyl	102.2	ox	266.1572	266.1565
VUF 4635	3	phenyl	126.7	ox	260.1108	260.1096
VUF 4636	3	benzyl	117.2	ox	274.1250	274.1252
VUF 4637	3	phenylethyl	125.5	ox	288.1414	288.1409

compound	n	R	melt. point (°C)	salt	ex. mass (measured)	ex.mass (calculated)
VUF 4681	4	ethyl	120.3	ox	226.1250	226.1252
VUF 4682	4	n-propyl	146.9	ox	240.1409	240.1409
VUF 4683	4	i-propyl	151.3	ox	240.1401	240.1409
VUF 4684	4	cyclohexyl	109.5	ox	280.1724	280.1722
VUF 4685	4	phenyl	153.7	ox	274.1251	274.1252
VUF 4686	4	benzyl	109.1	ox	288.1400	288.1409
VUF 4687	4	phenylethyl	130.8-132.2	ox	302.1560	302.1565
VUF 4613	5	methyl	111.0	ox	226.1251	226.1252
VUF 4614	5	ethyl	77.6	ox	240.1410	240.1409
VUF 4615	5	n-propyl	115.5-116.6	ox	254.1563	254.1565
VUF 4616	5	i-propyl	97.1	ox	254.1563	254.1565
VUF 4617	5	cyclohexyl	116.5	ox	294.1875	294.1878
VUF 4618	5	phenyl	108.9	ox	288.1402	288.1409
VUF 4619	5	benzyl	152.1-152.4	ox	302.1560	302.1565
VUF 4620	5	phenylethyl	118.5-119.5	ox	316.1716	316.1722
VUF 4740	6	methyl	106.5-110.0	ox		
VUF 4741	6	phenyl	121.0-125.5	ox		

EXAMPLE 5

Synthesis of N-benzyl-4-(1-dimethylsulfamoyl-5-imidazolyl)piperid-4-ol (VUF 4765).

10.0 g. of 1-(N,N-Dimethylsulfamoyl)imidazole (57 mmol) was dissolved in dry THF (150 ml) under an atmosphere of dry nitrogen and cooled to -70°C. n-Butyllithium in hexane (35 ml, 57 mmol) was added dropwise (temperature should not exceed -65°C). After 15 min, a solution of trimethylsilyl chloride (6.2 g, 57 mmol) in dry THF was added and the solution was stirred at room temperature for 1 h. The mixture was cooled to -70°C again and n-butyllithium in hexane (35 ml, 57 mmol) was added dropwise (temperature should not exceed -65°C). After 1 h, a solution of N-benzyl-4-piperidone (10.8 g, 5.7 mmol) in dry THF was added gradually and the mixture was allowed to (slowly) warm to room temperature overnight. The reaction mixture was poured into water and the THF was removed under reduced pressure. The product was extracted with $CHCl_3$ (3 x 150 ml), dried (Na_2SO_4) and concentrated in vacuo.

EXAMPLE 6

Synthesis of 4-(1-dimethylsulfamoyl-5-imidazolyl)piperid-4-ol (VUF 4764).

1.0 gram of VUF 4765 (2.7 mmol) was dissolved in methanol. 0.1 gram Pd/C (10%) and 1 gram of ammoniumformate (16 mmol) was added and the mixture was refluxed for one hour. After filtration the product was concentrated in vacuo.

EXAMPLE 7

Synthesis of 4-(4(5)-imidazolyl)1,2,3,6-tetrahydropyridine dihydrobromide (VUF 4736).

8.5 gram of VUF 4764 was dissolved in 30% HBr and refluxed for 16 hours. The solution was evaporated in vacuo and the residue was refluxed in absolute ethanol. A white precipitate was collected by centrifugation and washed with acetone (three times). The melting point was 271-275°C.

EXAMPLE 8

Synthesis of 4-(4(5)-imidazolyl)piperidine dihydrobromide (VUF 4735).

1.0 gram of VUF 4736 was dissolved in methanol, 0.1 gram Pd/C (10%) was added and this mixture was hygrogenated for 16 hours with 20 atm. of H_2 in an autoclave. The reaction mixture was filtrated, concentrated and washed with absolute ethanol. The melting point was 260-263°C.

EXAMPLE 9

Synthesis of 4-[(1-dimethylsulfamoyl-5-imidazolyl)methyl]-piperidine oxalate (VUF 4709)

1.0 g. of 1-(N,N-Dimethylsulfamoyl)imidazole (5.7 mmol) was dissolved in dry THF (50 ml) under an atmosphere of dry nitrogen and cooled to -70°C. n-Butyllithium in hexane (3.6 ml, 5.8 mol) was added dropwise (temperature should not exceed -65°C). After 15 min, a solution of tert-butyl-dimethylsilyl chloride (0.9 g, 5.7 mmol) in dry THF (15 ml) was added (5 min) and the solution was stirred at room temperature for 1 h. The mixture was cooled to -70°C again and n-butyllithium in hexane (3.6 ml, 5.8 mmol) was added dropwise (temperature should not exceed -65°C). After 0.5 h, a solution of 4-pyridinecarboxaldehyde (0.6 gram, 5.8 mol) in dry THF (15 ml) was added gradually and the mixture was allowed to (slowly) warm to room temperature overnight. The reaction mixture was poured into water (100 ml) and the THF was removed under reduced pressure. The product was extracted with CH_2Cl_2 (3 x 150 ml), dried (Na_2SO_4) and concentrated in vacuo.

11.53 gram (28.4 mmol) of the residue (made from a larger batch) was dissolved in 150 ml. of acetonitrile. 5.2 ml. of DBU (35 mmol) was added. 3.6 ml. acetic anhydride (38 mmol) was added after 10 min. and after 15 min. stirring at ambient temperature, the reaction mixture was concentrated in vacuo. The residue was dissolved in CH_2Cl_2 and washed with H_2O (three times). The organic layer was dried on Na_2SO_4 and concentrated in vacuo. The product was purified by a

column packed with flash-silicagel with ethylacetate as eluent (Rf on TLC = 0.51).

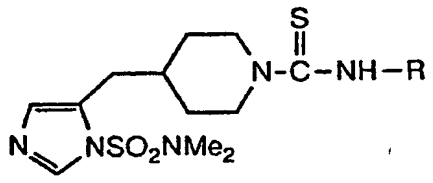
7.3 gram of the purified product (16.7 mmol) was dissolved in 50 ml. of acetic acid, 0.7 gram Pd/C (10%) was added and this mixture was hygrogenated for 16 hours with 50 atm. of H_2 in an autoclave. The reaction mixture was filtrated, concentrated and washed with absolute ethanol (2 times with 20 ml.). The hydrogenation was incomplete and repeated once more as described above.

The residue was dissolved in H_2O and the pH was raised to 12 by the addition of K_2CO_3 and extracted with CH_2Cl_2. The organic layer was dried with Na_2SO_4 , concentrated under reduced pressure and dissolved in ethylacetate. An excess of a saturated solution of oxalic acid in ethylacetate was added (slowly). The formed precipitate was collected by centrifugation and washed with ethylacetate (three times). The melting point was 120.8-121.1°C.

EXAMPLE 10

Synthesis N-substituted-N'-[4-[1-dimethylsulfamoyl-4(5)-imidazolyl)methyl]piperidine]thiourea.

Analogous to the preparation method of VUF 4740 from example 3, from VUF 4709, a number of compounds were synthesized with the formula :



The meaning of R, the melting points and the exact mass results are given in the table below.

compound	R	melt.point (°C)	ex.mass (measured)	ex.mass (calculated)
VUF 4711	methyl	131.7-134.5		
VUF 4712	cyclo-hexyl	137.10138.8		

EXAMPLE 11

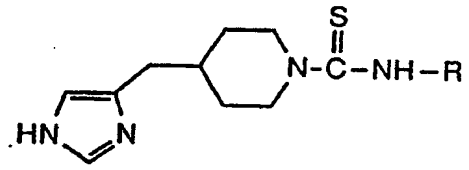
Synthesis of 4-[(4(5)-imidazolyl)methyl]piperidine dihydrobromic acid (VUF 4708).

5.5 gram (16.5 mmol) of VUF 4709 was refluxed in 30% HBr for 16 hours. The solution was concentrated under reduced pressure and the residue was dissolved and refluxed in absolute ethanol for one hour. This mixture was concentrated in vacuo and washed with acetone (three times). The white crystals were collected and the melting point was 221.1-222.7°C.

EXAMPLE 12

Synthesis of N-substituted-N'-[4-[4(5)-imidazolyl)methyl]-piperidine]thiourea.

Analogous to the preparation method of VUF 4740 from example 3, from VUF 4708, a number of compounds were synthesized with the formula :



The meaning of R, the melting points and the exact mass results are given in the table below.

compound	R	melt. point (C°)	salt
VUF 4713	methyl		ox.
VUF 4714	cyclo-hexyl	159.8-160.2	HBr

Table 1. ^1H NMR results of the compounds mentioned in the description.

VUF 4577 (D_2O): δ 2.87 (s, 3H, CH_3), 3.03 (t, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 3.78 (t, 2H, J=7 Hz,

$C\underline{H}_2NH$), 7.30 (s, 1H, imidazole-5(4)H), 8.62 (s, 1H, imidazole-2H) ppm.

VUF 4578 (D_2O): δ 1.12 (t, 3H, J=7 Hz, CH_3), 3.03 (t, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 3.32(q, 2H, J=7 Hz, $C\underline{H}_2CH_3$), 3.78 (t, 2H, J=7 Hz, $C\underline{H}_2NH$), 7.39 (s, 1H, imidazole-5(4)H), 8.62 (s, 1H, imidazole-2H) ppm

VUF 4579 (D_2O): δ 0.88 (t, 3H, J=7 Hz, CH_3), 1.53 (m, 2H, $C\underline{H}_2CH_3$), 3.04 (t, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 3.10-3.45 (m, 2H, $C\underline{H}_2CH_2CH_3$), 3.70-3.92 (m, 2H, $C\underline{H}_2NH$), 7.30 (s, 1H, imidazole-5(4)H), 8.64 (s, 1H, imidazole-2H) ppm.

VUF 4580 (D_2O): δ 1.01 (d, 6H, J=7 Hz, 2*CH_3), 2.90 (t, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 3.58-3.75 (m, 2H, $C\underline{H}_2NH$), 3.75-4.10 (b s, 1H, CH), 7.16 (s, 1H, imidazole-5(4)H), 8.49 (s, 1H, imidazole-2H) ppm.

VUF 4581 (D_2O): δ 0.99-1.85 (m, 10H, CH_2), 2.97 (t, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 3.50-3.90 (m, 3H, CH and $C\underline{H}_2NH$), 7.22 (s, 1H, imidazole-5(4)H), 8.53 (s, 1H, imidazole-2H) ppm.

VUF 4582 (D_2O): δ 2.94-3.03 (m, 2H, imidazole-$C\underline{H}_2$), 3.75-3.97 (m, 2H, $C\underline{H}_2NH$), 7.11-7.57 (m, 6H, phenyl-H and imidazole-5(4)H), 8.61 (s, 1H, imidazole-2H) ppm.

VUF 4583 (DMSO-d_6): δ 2.89 (t, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 3.59-3.83 (m, 2H, $C\underline{H}_2NH$), 4.53-4.77 (m, 2H, $C\underline{H}_2$-phenyl), 7.18-7.38 (m, 6H, phenyl-H and imidazole-4(5)H), 7.85-8.00 (m, 1H, NH), 8.72 (t, 1H, J=6 Hz, NH),

8.72 (s, 1H, imidazole-2H), 11.15-11.85 (m, NH and oxalate) ppm.

VUF 4584 (D_2O): δ 2.66-2.91 (m, 4H, imidazole-$C\underline{H}_2$ and $C\underline{H}_2$-phenyl), 3.32-3.80 (m, 4H, $C\underline{H}_2NH$ and $C\underline{H}_2CH_2$-phenyl), 7.15 (s, 1H, imidazole-5(4)H), 7.10-7.34 (m, 5H, phenyl-H), 8.47 (s, 1H, imidazole-2H) ppm.

VUF 4613 (D_2O): δ 1.31 (m, 2H, $(CH_2CH_2)_2C\underline{H}_2$), 1.62 (m, 4H, $(CH_2C\underline{H}_2)_2CH_2$), 2.67 (t, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 2.82 (m, 3H, $C\underline{H}_3$), 3.33 (m, 2H, $C\underline{H}_2NH$), 7.14 (s, 1H, imidazole-5(4)H), 8.50 (s, 1H, imidazole-2H) ppm.

VUF 4614 (D_2O): δ 1.12 (t, 3H, J=7 Hz, $C\underline{H}_3$), 1.35 (m, 2H, $(CH_2CH_2)_2C\underline{H}_2$), 1.65 (m, 4H, $(CH_2C\underline{H}_2)_2CH_2$), 2.72 (t, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 3.47 (m, 4H, $C\underline{H}_2NH$), 7.19 (s, 1H, imidazole-5(4)H), 8.55 (s, 1H, imidazole-2H) ppm.

VUF 4615 (D_2O): δ 0.82 (t, 3H, J=7 Hz, $C\underline{H}_3$), 1.30 (m, 4H, $(CH_2CH_2)_2C\underline{H}_2$) + $C\underline{H}_2CH_3$), 1.60 (m, 4H, $(CH_2C\underline{H}_2)_2CH_2$), 2.67 (t, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 3.30 (m, 4H, $C\underline{H}_2NH$), 7.13 (s, 1H, imidazole-5(4)H), 8.50 (s, 1H, imidazole-2H) ppm.

VUF 4616 (D_2O): δ 1.08 (s, 6H, $C\underline{H}_3$), 1.28 (m, 2H, $(CH_2CH_2)_2C\underline{H}_2$), 1.57 (m, 4H, $(CH_2C\underline{H}_2)_2CH_2$), 2.65 (t, 2H, imidazole-$C\underline{H}_2$), 3.32 (m, 2H, $C\underline{H}_2NH$), 4.00 (m, 1H, $C\underline{H}$), 7.13 (s, 1H, imidazole-5(4)H), 8.47 (s, 1H, imidazole-2H) ppm.

VUF 4617 (D_2O): δ 1.05-2.05 (m, 16H, $(CH_2CH_2)_2CH_2$ + $(CH_2CH_2)_2CH_2$ + cyclohexyl-CH_2), 2.73 (t, 2H, J=7 Hz, imidazole-CH_2), 3.43 (m, 3H, CH_2NH + CHNH), 7.22 (s, 1H, imidazole-5(4)H), 8.58 (s, 1H, imidazole-2H) ppm.

VUF 4618 (D_2O): δ 1.35 (m, 2H, $(CH_2CH_2)_2CH_2$), 1.67 (m, 4H, $(CH_2CH_2)_2CH_2$), 2.75 (t, 2H, J=7 Hz, imidazole-CH_2), 3.53 (m, 2H, CH_2NH), 7.37 (m, 6H, imidazole-5(4)H + phenyl-H), 8.59 (s, 1H, imidazole-2H) ppm.

VUF 4619 (D_2O): δ 1.27 (m, 2H, $(CH_2CH_2)_2CH_2$), 1.60 (m, 4H, $(CH_2CH_2)_2CH_2$), 2.67 (t, 2H, J=7 Hz, imidazole-CH_2), 3.43 (m, 2H, CH_2NH), 4.63 (m, 2H, CH_2-phenyl), 7.17 (s, 1H, imidazole-5(4)H), 7.36 (m, 5H, phenyl-H), 8.53 (s, 1H, imidazole-2H) ppm.

VUF 4631 (D_2O): δ 1.12 (t, 3H, J=7 Hz, CH_3), 1.95 (m, 2H, CH_2CH_2NH), 2.77 (t, 2H, J=8 Hz, imidazole-CH_2), 3.15-3.62 (m, 4H, CH_2NH), 7.23 (s, 1H, imidazole-5(4)H), 8.57 (s, 1H, imidazole-2H) ppm.

VUF 4632 (D_2O): δ 0.87 (t, 3H, J=7 Hz, CH_3), 1.53 (m, 2H, CH_2CH_3), 1.97 (m,2H, CH_2CH_2NH), 2.77 (t, 2H, J=7 Hz, imidazole-CH_2), 3.10-3.65 (m, 4H, CH_2NH), 7.23 (s, 1H, imidazole-5(4)H), 8.56 (s, 1H, imidazole-2H) ppm.

VUF 4633 (D_2O): δ 1.13 (d, 6H, J=7 Hz, CH_3), 1.94 (m, 2H, CH_2CH_2NH), 2.77 (t, 2H, J=7 Hz, imidazole-CH_2), 3.37-3.58 (m, 2H,

$C\underline{H}_2NH$), 3.89-4.17 (m, 1H, CH), 7.23 (s, 1H, imidazole-5(4)H), 8.57 (s, 1H, imidazole-2H) ppm.

VUF 4634 (D_2O): δ 0.93-1.97 (m, 12H, $C\underline{H}_2CH_2NH$ + 5*CH_2), 2.70 (t, 2H, J=8 Hz, imidazole-$C\underline{H}_2$), 3.23-3.90 (m, 3H, $C\underline{H}_2NH$ + $C\underline{H}NH$), 7.18 (s, 1H, imidazole-5(4)H), 8.52 (s, 1H, imidazole-2H) ppm.

VUF 4635 (D_2O): δ 1.90 (m, 2H, $C\underline{H}_2CH_2NH$), 2.70 (t, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 3.39-3.65 (m, 2H, $C\underline{H}_2NH$), 7.27 (s, 1H, imidazole-5(4)H), 8.50 (s, 1H, imidazole-2H) ppm.

VUF 4636 (D_2O): δ 1.84 (m, 2H, $C\underline{H}_2CH_2NH$), 2.39-2.79 (m, 2H, imidazole-$C\underline{H}_2$), 3.30-3.57 (m, 2H, $C\underline{H}_2NH$), 4.42-4.73 (m, 2H, CH_2-phenyl), 7.10 (s, 1H, imidazole-5(4)H), 7.29 (m, 5H, phenyl-H), 8.47 (s, 1H, imidazole-2H) ppm.

VUF 4637 (D_2O): δ 1.73 (m, 2H, $C\underline{H}_2CH_2NH$), 2.58 (t, 2H, J=8 Hz, imidazole-$C\underline{H}_2$), 2.82 (t, 2H, J=7 Hz, $C\underline{H}_2$-phenyl), 3.10-3.44 (m, 2H, $C\underline{H}_2NH$), 3.44-3.79 (m, 2H, $C\underline{H}_2CH_2$-phenyl), 7.12 (s, 1H, imidazole-5(4)H), 7.16-7.36 (m, 5H, phenyl-H), 8.49 (s, 1H, imidazole-2H) ppm.

VUF 4681 (D_2O): δ 1.08 (t, 3H, J=7Hz, $C\underline{H}_3$), 1.61 (m, 4H, $CH_2C\underline{H}_2$), 2.72 (t, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 3.22-3.51 (m, 4H, $C\underline{H}_2NH$), 7.17 (s, 1H, imidazole-5(4)H), 8.52 (s, 1H, imidazole-2H) ppm.

VUF 4682 (D_2O): δ 0.84 (t, 3H, J=7Hz, CH_3), 1.42-1.78 (m, 6H, CH_2CH_3 + CH_2CH_2), 2.73 (t, 2H, J=7 Hz, imidazole-CH_2), 3.10-3.62 (m, 4H, CH_2NH), 7.18 (s, 1H, imidazole-5(4)H), 8.53 (s, 1H, imidazole-2H) ppm.

VUF 4683 (D_2O): δ 1.16 (d, 6H, J=7 Hz, CH_3), 1.65 (m, 4H, CH_2CH_2), 2.76 (t, 2H, J=7 Hz, imidazole-CH_2), 3.43 (m, 2H, CH_2NH), 4.08 (m, 1H, CH), 7.21 (s, 1H, imidazole-5(4)H), 8.55 (s, 1H, imidazole-2H) ppm.

VUF 4684 (DMSO-d_6): δ 1.00-1.95 (m, 14H, CH_2CH_2 + cyclohexyl-CH_2), 2.64 (m, 2H, imidazole-CH_2), 3.37 (m, 2H, CH_2NH), 3.93 (m, 1H, CH_3), 7.20 (s, 1H, imidazole-5(4)H), 7.28-7.62 (m, 4H, NH + CO_2H), 8.50 (s, 1H, imidazole-2H) ppm.

VUF 4685 (D_2O): δ 1.59 (m, 4H, CH_2CH_2), 2.70 (t, 2H, imidazole-CH_2), 3.49 (m, 2H, CH_2NH), 7.31 (m, 6H, imidazole-5(4)H + phenyl-H), 8.50 (s, 1H, imidazole-2H) ppm.

VUF 4686 (DMSO-d_6): δ 1.53 (m, 4H, CH_2CH_2), 2.59 (t, 2H, J=7 Hz, imidazole-CH_2), 3.40 (m, 2H, CH_2NH), 4.63 (m, 2H, CH_2-benzyl), 7.13 (s, 1H, imidazole-5(4)H), 7.28 (m, 5H, phenyl-H), 7.71 (m, 1H, N-H), 7.99 (m, 1H, N-H), 8.39 (s, 1H, imidazole-2H) ppm.

VUF 4687 (DMSO-d_6): δ 1.55 (m, 4H, CH_2CH_2), 2.62 (t, 2H, J=7 Hz, imidazole-CH_2), 2.78 (t, 2H, J=7 Hz, CH_2-phenyl), 3.37 (m, 2H, CH_2NH), 3.57

(m, 2H, $C\underline{H}_2CH_2$-phenyl), 7.27 (m, 6H, imidazole-5(4)H + phenyl-H), 7.63 (m, 2H, N-H), 8.67 (s, 1H, imidazole-2H) ppm.

VUF 4701 (D_2O): δ 1.77 (m, 4H, $C\underline{H}_2C\underline{H}_2$), 2.80 (t, 2H, J=8 Hz, imidazole-4(5)-$C\underline{H}_2$), 3.06 (t, 2H, J=8 Hz, $C\underline{H}_2NH$), 7.28 (s, 1H, imidazole-5(4)H), 8.59 (s, 1H, imidazole-2H) ppm.

VUF 4702 (D_2O): δ 1.37 (m, 2H, $(CH_2CH_2)_2C\underline{H}_2$), 1.63 (m, 4H, $(CH_2C\underline{H}_2)_2CH_2$), 2.68 (t, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 2.93 (t, 2H, J=7 Hz, $C\underline{H}_2NH$), 7.16 (s, 1H, imidazole-5(4)H), 8.49 (s, 1H, imidazole-2H) ppm.

VUF 4708 (D_2O): δ 1.48 (qd, 2H, J=13, 3 Hz, 3,5-H_ax), 1.94 (dm, 2H, J= 13 Hz, 3,5-H_eq), 2.00 (m, 1H, 4-H), 2.72 (d, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 2.98 (tm, 2H, J=13 Hz, 2,6-H_ax), 3.41 (dm, 2H, J=13 Hz, 2,6-H_eq), 7.28 (s, 1H, imidazole-5(4)H), 8.59 (s, 1H, imidazole-2H) ppm.

VUF 4709 (D_2O): δ 1.47 (qm, 2H, J=13 Hz, 3,5-H_ax), 1.97 (dm, 2H, J=14 Hz, 3,5-H_eq), 2.03 (m, 1H, 4-H), 2.87 (d, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 2.97 (tm, 2H, J=13 Hz, 2,6-H_ax), 3.04 (s, 6H, $N(C\underline{H}_3)_2$), 3.42 (dm, 2H, J=13 Hz, 2,6 H_eq), 7.43 (s, 1H, imidazole-5H), 9.16 (s, 1H, imidazole-2H) ppm.

VUF 4711 ($CDCl_3$): δ 1.18 (qm, 2H, J=13 Hz, 3,5-H_ax), 169 (dm, 2H, J=13 Hz, 3,5-H_eq), 1,88 (m, 2H, 4-H), 2.62 (d, J=7 Hz, imidazole-$C\underline{H}_2$), 2.82 (s, 6H, $N(C\underline{H}_3)_2$), 2.90 (tm, 2H,

J=13 Hz, 2,6-H_ax), 3.07 (d, 3H, J=6 Hz, $C\underline{H}_3$), 4.58 (dm, 2H, J=13 Hz, 2,6-H_eq), 6.04 (m, 1H, NH), 6.76 (s, 1H, imidazole-5H), 7.80 (s, 1H, imidazole-2H) ppm.

VUF 4712 ($CDCl_3$): δ 0.98-2.10 (m, 15H, $C\underline{H}(C\underline{H}_2CH_2)_2NH$ + $(C\underline{H}_2)_5$), 2.63 (d, 2H, J=7Hz, Imidazole-$C\underline{H}_2$), 2.82 (s, 6H, $N\underline{Me}_2$), 2,88 (tm, 2H, J=13 Hz, 2,6-H_ax(pip)), 4.27 (m, 1H, NHC$\underline{H}$), 4.54 (dm, 2H, J=13Hz, 2,6-H_eq(pip)), 5.46 (d, 1H, J=7Hz, N$\underline{H}$), 6.78 (s, 1H, Imidazole-5 H), 7.80 (s, 1H, (Imidazole-2 H)) ppm.

VUF 4713 (D_2O): δ 1.04-1.32 (m, 2H, 3,5-H_ax), 1.72 (dm, 2H, J=14Hz, 3,5-H_eq), 1,97 (m, 1H, 4-H), 2.64 (d, 2H, J=7Hz, Imidazole-$C\underline{H}_2$), 3,01 (s, 3H, $C\underline{H}_3$), 3,06 (tm, 2H, J=14 Hz, 2,6-H_ax), 4.48 (dm, 2H, J=13Hz, 2,6-H_eq), 7.12 (s, 1H, Imidazole-4(5)H), 8.28 (s, 1H, Imidazole-2H) ppm.

VUF 4714 (D_2O): δ 0.98-2.10 (m, 15H, $C\underline{H}(C\underline{H}_2CH_2)_2NH$ + $(C\underline{H}_2)_5$), 2.67 (d, 2H, J=7Hz, Imidazole-$C\underline{H}_2$), 3,00 (tm, 2H, J=13 Hz, 2,6-H_ax(pip)), 4.10 (m, 1H, NHC$\underline{H}$), 4.48 (dm, 2H, J=13Hz, 2,6-H_eq(pip)), 7.22 (s, 1H, Imidazole-4(5)H), 8.54 (s, 1H, Imidazole-2H) ppm.

VUF 4732 (D_2O): δ 1.33 (m, 4H, $(CH_2CH_2)_2(C\underline{H}_2)_2$), 1.61 (m, 4H, $(CH_2C\underline{H}_2)_2CH_2CH_2$), 2.68 (t, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 2.93 (t, 2H, J=7 Hz, $C\underline{H}_2NH$), 7.14 (s, 1H, imidazole-5(4)H), 8.50 (s, 1H, imidazole-2H) ppm.

VUF 4733 (D_2O): δ 1.38 (m, 8H, $(CH_2CH_2)_2(C\underline{H}_2)_4$), 1.60 (m, 4H, $(CH_2C\underline{H}_2)_2(CH_2)_4$), 2.66 (t, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 2.93 (t, 2H, J=7 Hz, $C\underline{H}_2NH$), 7.13 (s, 1H, imidazole-5(4)H), 8.49 (s, 1H, imidazole-2H) ppm.

VUF 4734 (D_2O): δ 1.27 (m, 12H, $(CH_2CH_2)_2(C\underline{H}_2)_6$), 1.62 (m, 4H, $(CH_2C\underline{H}_2)_2(CH_2)_6$), 2.67 (t, 2H, J=7 Hz, imidazole-$C\underline{H}_2$), 2.94 (t, 2H, J=7 Hz, $C\underline{H}_2NH$), 7.14 (s, 1H, imidazole-5(4)H), 8.50 (s, 1H, imidazole-2H) ppm.

VUF 4735 (D_2O): δ 2,03 (m, 2H, 3,5-H_ax), 2,39 (dm, 2H, J=13 Hz, 3,5-H_eq), 3.29 (m, 3H, 2,6-H_ax + 4-H), 3,63 (dm, 2H, J=13 Hz, 2,6 H_eq), 7.48 (s, 1H, imidazole-5(4)H), 8.77 (s, 1H, imidazole-2H) ppm.

VUF 4736 (D_2O): δ 2.72 (s, 2H, $C\underline{H}_2$-CH_2-N), 3.56 (t, 2H, J = 7 Hz, N-$C\underline{H}_2$-CH_2), 3.98 (s, 2H, N-$C\underline{H}_2$-CH), 6.36 (s, 1H, CH), 7.59 (s, 1H, imidazole-4(5)H), 8.73 (s, 1H, imidazole-2H) ppm.

VUF 4740 (D_2O): δ 1.20-1.78 (m, 8H, CH2-$(C\underline{H}_2)_4$-CH_2), 2.72 (t, 2H, J = 7Hz, imidazole-$C\underline{H}_2$), 2.90 (s, 3H, $C\underline{H}_3$), 3.18-3.58 (m, 2H, $C\underline{H}_2NH$), 7.18 (s, 1H, imidazole-4(5)H), 8.53 (s, 1H, imidazole- 2H) ppm.

VUF 4741 (D_2O): δ 1.22-1.79 (m, 8H, im-CH_2-$(CH_2)_4$-CH_2), 2.70 (t, 2H, J = 7 Hz, imidazole-$C\underline{H}_2$), 3.34-3.59 (m, 2H, $C\underline{H}_2NH$), 7.09-7.52 (m, 6H, phenyl-H + imidazole-4(5)H), 8.50 (s, 1H, imidazole-2H) ppm.

VUF 4764 (D_2O): δ 2.12-2.28 (m, 4H, $C\underline{H}_2CH_2NH$), 2.79 (s, 6H, $(C\underline{H}_3)_2N$), 3.36-3.56 (m, 5H, $CH_2C\underline{H}_2NH$

+ C<u>H</u>OH), 4.36 (s, 2H, CH_2-phenyl), 7.40 (s, 1H, imidazole-5H), 7.48 (s, 5H, phenyl-H), 8.64 (s, 1H, imidazole-2H) ppm.

VUF 4765 (D_2O): δ 1.98-2.31 (m, 4H, C<u>H</u>$_2$CH_2NH), 2.52 (s, 6H, (C<u>H</u>$_3$)$_2$N), 3.16-3.42 (m, 5H, CH_2C<u>H</u>$_2$NH + C<u>H</u>OH), 7.17 (s, 1H, imidazole-5H), 7.87 (s, 1H, imidazole-2H) ppm.

Pharmacological experiments

The agonistic and antagonistic activities on the histamine H_3 receptor of the various compounds were determined with a test system, described in Vollinga et al., Meth. Find. Clin. Exp. Pharmacol., 14(10), p. 747-751 (1992).

The results of the experiments are given in the tables 2 and 3 below. pD_2 is the negative value of the concentration of the test compound at which 50% agonistic activity was measured. pA_2 is the negative logarithm of the concentration of the testcompound at which the concentration of the agonist had to be doubled to obtain the same effect as obtained when the antagonist was absent.

Pharmaceutical compositions, comprising compounds of formula I as the active ingredient for therapeutically influencing the human and animal histaminergic system have the form of powders, suspensions, solutions, sprays, emulsions, unguents or creams and can be used for local application, intranasal, rectal, vaginal and also for oral or parenteral (intravenous, intradermal, intramuscular, intrathecal etc.) administration. Such compositions can be prepared by combining (i.e. by mixing, dissolving etc.) of the active compound of formula I in the form of a free acid or salt with pharmaceutically acceptable excipients with neutral character (such aquous or non-aquous solvents, stabilizers, emulsifiers, derergents, additives), and further if neccesary colouring agents and flavouring agents.

The concentration of the active ingredient in a pharmaceutical composition can vary between 0.1% and 100%, depending on the nature of the influence and the method of administration. The dose of the active ingredient that is administered can further be varied between 0.1 mg and 100 mg per kg bodyweight.

Table 2. Antagonistic activity

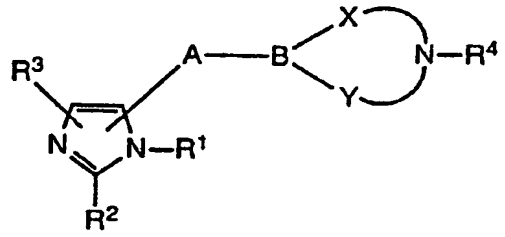
Compound	pA_2
VUF 4613	8.0
VUF 4614	8.0
VUF 4615	7.7
VUF 4616	7.7
VUF 4617	7.5
VUF 4618	7.6
VUF 4619	7.7
VUF 4620	7.5
VUF 4680	7.0
VUF 4681	7.5
VUF 4682	7.4
VUF 4683	7.5
VUF 4684	7.2
VUF 4685	7.6
VUF 4686	6.8
VUF 4687	7.0
VUF 4701	7.7
VUF 4702	8.4
VUF 4732	7.8
VUF 4733	6.0
VUF 4734	6.0
VUF 4740	8.0
VUF 4741	7.9

Table 3. Agonistic activity

Compound	pD_2
VUF 4708	8.0

CLAIMS

1. Imidazole-derivatives of the general formula:

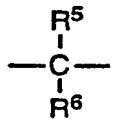


(I)

wherein :

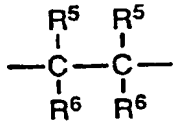
A is

1) a group of the formula $(CH_2)_m$, wherein m = 0-9; or
2) a group of the formula:



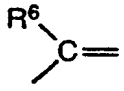
wherein R^5 represents hydrogen, (C_1-C_3)alkyl-, aryl(C_1-C_3)alkyl-, aryl-, wherein aryl may optionally be substituted, hydroxyl-, (C_1-C_3)alkoxy-, halogen, amino-, cyano- or nitro; and R^6 represents hydrogen, (C_1-C_3)alkyl-, aryl(C_1-C_3)alkyl-, or aryl-, wherein aryl may optionally be substituted; or

3) a group of the formula:

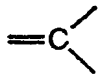


wherein R^5 and R^6 are as defined above; or

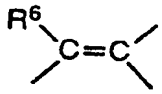
4) a group of the formula:



if B is a group of the formula:

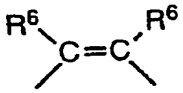


such that A and B together form a group of the formula:



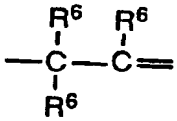
wherein R^6 is as defined above; or

5) a group of the formula:

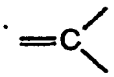


wherein R^6 is as defined above; or

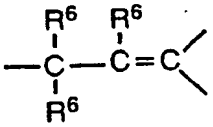
6) a group of the formula:



if B is a group of the formula:

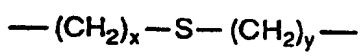


such that A and B together form a group of the formula:



wherein R^6 is as defined above; or

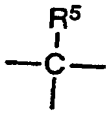
7) a group of the formula:



wherein x+y = m-1;

B is

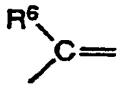
1) a group of the formula:



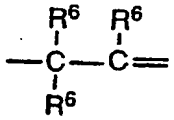
wherein R^5 is as defined above; or

2) a group of the formula:

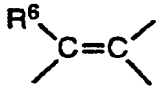
if A is a group of one of the formulas:



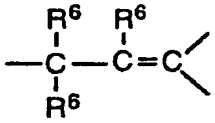
or



such that A and B together form a group of one of the formulas:



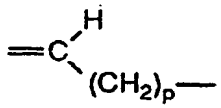
or



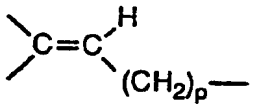
wherein R^6 is as defined above; or

3) a group of the formula:

if X is a group of the formula:



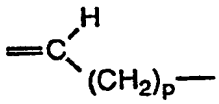
such that B and X together form a group of the formula



wherein p = 1-3; or

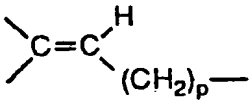
X is

1) a group of the formula $(CH_2)_n$, wherein n = 2-4; or
2) a group of the formula:



if B is a group of the formula:

such that X and B together form a group of the formula:



wherein p = 1-3; or

3) two hydrogens (one on the carbon and one on the nitrogen); or

4) one hydrogen on the carbon atom and one R^7 group on the nitrogen atom,
wherein R^7 represents hydrogen, (C_1-C_{10})alkyl-, aryl(C_1-C_{10})alkyl-, or aryl, wherein aryl may optionally be substituted;

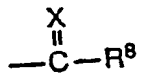
Y is a group of the formula $(CH_2)_k$, wherein k = 0-2;

R^1 represents hydrogen, (C_1-C_3)alkylsulfonamide-, (C_1-C_3)-alkyl-, aryl(C_1-C_3)alkyl- or aryl, wherein aryl may optionally be substituted;

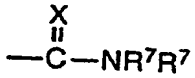
R^2 represents hydrogen, (C_1-C_{10})alkylsilyl-, (C_1-C_3)alkyl-, aryl(C_1-C_3)alkyl- or aryl, wherein aryl may optionally be substituted;

R^3 represents hydrogen, halogen, amino-, nitro-, hydroxyl-, mercaptan, (C_1-C_3)alkoxy-, (C_1-C_3)alkylsulfide-;

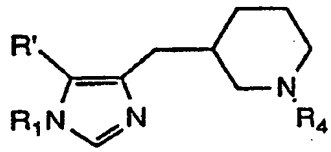
R^4 represents hydrogen, (C_1-C_{10})alkyl-, (C_1-C_3)alkyl-sulfonamide-, aryl(C_1-C_{10})alkyl-, aryl, wherein aryl may optionally be substituted;
or a group of the formula :

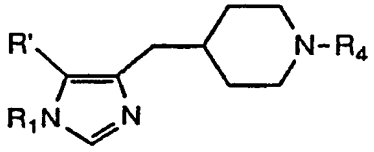


or a group of the formula :

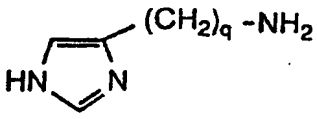


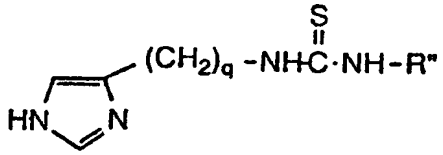
wherein X represents O, S, or NH,
R^7 is as defined as above;
R^8 represents (C_1-C_{10})alkyl-, aryl(C_1-C_{10})alkyl- or aryl, wherein aryl may optionally be substituted and
wherein aryl is phenyl, substituted phenyl, naphtyl, substituted naphtyl, pyridyl;
or pharmacological acceptable salts thereof,
excluding derivatives of one of the formulas:



or


wherein R' is hydrogen, methyl, ethyl;
and derivatives of the formulas:

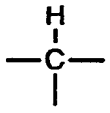


or


wherein q is 2-5 and R" is hydrogen, (C_1-C_3)alkyl, aryl or aryl(C_1-C_3)alkyl.

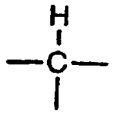
2. Imidazole derivatives of formula I, wherein A is a group of the formula $(CH_2)_m$, wherein m = 1-9, and

1) when X represents two hydrogens (one on the carbon and one on the nitrogen);
B represents a group of the formula:



Y represents a group of the formula $(CH_2)_k$, wherein k = 0; or

2) when X represents one hydrogen on the carbon atom and one R^7 group on the nitrogen atom,
wherein R^7 is as defined in claim 1;
B represents a group of the formula:



Y represents a group of the formula $(CH_2)_k$, wherein k = 0; and

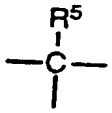
R^2 represents hydrogen, (C_1-C_3)alkyl-, aryl-(C_1-C_3)alkyl- or aryl, wherein aryl may optionally be substituted;

R^3 represents hydrogen; and

R^1 and R^4 are as defined in claim 1.

3. Imidazole derivatives of formula I, wherein A is a group of the formula $(CH_2)_m$, wherein m = 0, and

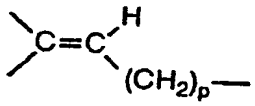
1) when B is a group of the formula:



wherein R^5 is as defined in calim 1;

X represents a group of the formula $(CH_2)_n$, wherein n = 2-4 and Y represents a group of the formula $(CH_2)_k$, wherein k = 0-2, with the restriction that n+k = 3 or 4; or

2) when B and X together form a group of the formula:



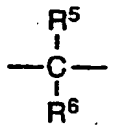
wherein p = 1-3,

Y represents a group of the formula $(CH_2)_k$, wherein k = 0-2, with the restriction that p+k = 2 or 3;

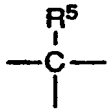
R^3 represents hydrogen; and

R^1, R^2 and R^4 are as defined in claim 1.

4. Imidazole derivatives of formula I, wherein: when A is a group of the formula:

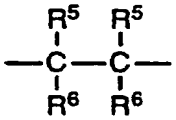


wherein R^5 and R^6 are as defined in claim 1;
B represents a group of the formula:

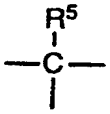


wherein R^5 is as defined in claim 1;
X represents a group of the formula $(CH_2)_n$, wherein n = 2-4;
and
Y represents a group of the formula $(CH_2)_k$, wherein k = 0-2,
with the restriction that n+k = 3 or 4; and
R^1, R^2, R^3 and R^4 are as defined in claim 1.

5. Imidazole derivatives of formula I, wherein
A is a group of the formula:

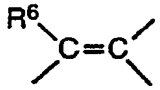


wherein R^5 and R^6 are as defined in claim 1;
B represents a group of the formula:



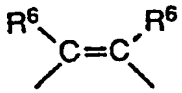
wherein R^5 is as defined in claim 1;
X represents a group of the formula $(CH_2)_n$, wherein n = 2-4;
Y represents a group of the formula $(CH_2)_k$, wherein k = 0-2,
with the restriction that n+k = 3 or 4;
R^3 represents hydrogen; and
R^1, R^2 and R^4 are as defined in claim 1.

6. Imidazole derivatives of formula I, wherein when A and B together form a group of the formula:

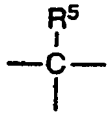


wherein R^6 is as defined in claim 1;
X represents a group of the formula $(CH_2)_n$, wherein n = 2-4;
Y represents a group of the formula $(CH_2)_k$, wherein k = 0-2, with the restriction that n+k = 3 or 4;
R^3 represents hydrogen; and
R^1, R^2 and R^4 are as defined in claim 1.

7. Imidazole derivatives of formula I, wherein when A is a group of the formula:

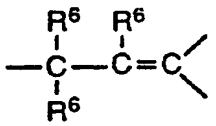


wherein R^6 is as defined in claim 1;
B represents a group of the formula:



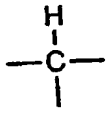
wherein R^5 is as defined in claim 1;
X represents a group of the formula $(CH_2)_n$, wherein n = 2-4;
Y represents a group of the formula $(CH_2)_k$, wherein k = 0-2, with the restriction that n+k = 3 or 4;
R^3 represents hydrogen; and
R^1, R^2 and R^4 are as defined in claim 1.

8. Imidazole derivatives of formula I, when A and B together form a group of the formula:

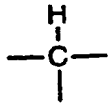


wherein R^6 is as defined above;
X represents a group of the formula $(CH_2)_n$, wherein n = 2-4;
Y represents a group of the formula $(CH_2)_k$, wherein k = 0-2,
with the restriction that n+k = 3 or 4;
R^3 represents hydrogen; and
R^1, R^2 and R^4 are as defined in claim 1.

9. Imidazole derivatives of formula I, wherein
A is a group of the formula - $(CH_2)_x$ - S - $(CH_2)_x$ -, wherein
x+y = m-1, and
1) when X represents two hydrogens (one on the carbon and one on the nitrogen);
B represents a group of the formula:



Y represents a group of the formula $(CH_2)_k$, wherein
k = 0; or
2) when X represents one hydrogen on the carbon atom and one R^7 group on the nitrogen atom,
wherein R^7 is as defined in claim 1;
B represents a group of the formula:



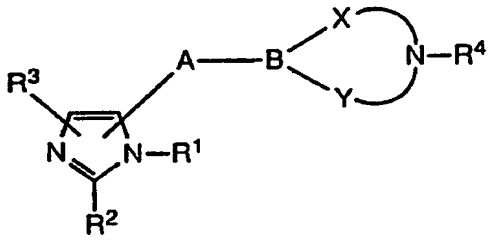
Y represents a group of the formula $(CH_2)_k$, wherein
k = 0; and
R^2 represents hydrogen, (C_1-C_3)alkyl-, aryl-(C_1-C_3)alkyl- or aryl, wherein aryl may optionally be substituted;

R^3 represents hydrogen; and

R^1 and R^4 are as defined in claim 1.

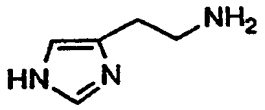
10. Imidazole derivative as claimed in claim 2 having the formula/wherein the derivative is N-methyl-N'-[6-(4(5)-imidazolyl)hexyl]thiourea.

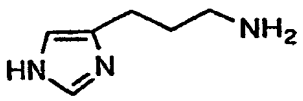
11. Pharmaceutical composition having agonistic or antagonistic activity on the histamine H_3-receptor comprising a suitable excipient and as the active ingredient an imidazole derivative of the formula I

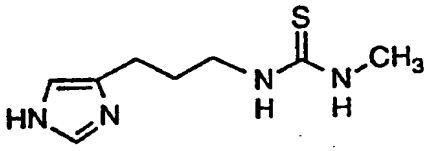


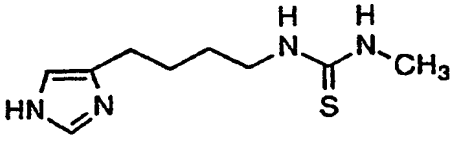
(I)

wherein the substituents are as defined in claim 1, excluding the derivatives of the formulas

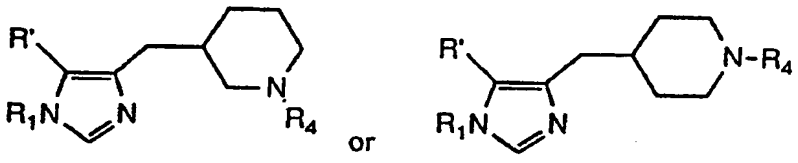






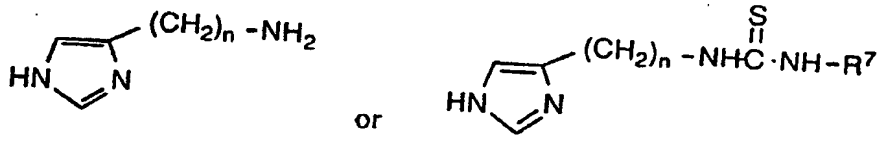


and derivatives of the formulas



wherein R' is hydrogen, methyl, ethyl;

12. Pharmaceutical composition as claimed in claim 11, wherein the active ingredient is a derivative of the formulas



wherein n is 5 or 6 and R^7 is hydrogen, (C_1-C_{10})alkyl-, aryl(C_1-C_{10})alkyl-, or aryl, wherein aryl may be optionally be substituted.

13. Pharmaceutical composition as claimed in claim 11 or 12, wherein the active ingredient is 4(5)-(5-aminopentyl)-imidazole or 4(5)-(6-aminohexyl)-imidazole.

14. Pharmaceutical composition as claimed in claim 11 or 12, wherein the active ingredient is N-methyl-N'-[5-(4(5)-imidazolyl)pentyl]thiourea or N-methyl-N'-[6-(4(5)-imidazolyl)hexyl]thiourea.

15. Pharmaceutical composition as claimed in claim 11 or 12, wherein the active ingredient is 4-(4(5)-imidazolyl-methyl)piperidine.

16. Method of preparing imidazole derivatives as defined in claim 11, by C5-lithiation of a 1,2-diprotected imidazole and subsequent treatment thereof with a suitable electrophile.

17. Method as claimed in claim 16, wherein the electrophile is a halogen, aldehyde, keton, nitrile, epoxide or acylhalide.

18. Use of the derivatives as defined in claim 11 as a biological active agent.

19. Use of the derivatives as defined in claim 11 as an agent having agonistic or antagonistic activity on the histamine H_3-receptor.

20. Use of derivatives as defined in claim 11 as a pharmaceutical composition showing agonistic or antagonistic activity on the histamine H_3-receptor.

21. Use of the derivatives as defined in claim 11 as a medicament for the treatment of H_3-receptor related disorders.

22. Use of the derivatives as defined in claim 11 for the preparation of a pharmaceutical composition showing agonistic or antagonistic activity on the histamine H_3-receptor.

23. Use of the derivatives as defined in claim 11 for the preparation of a medicament for the treatment of H_3-receptor related disorders.

INTERNATIONAL SEARCH REPORT

Intern. ..nal Application No
PCT/NL 94/00206

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D233/54 C07D401/04 C07D401/06 A61K31/415

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 197 840 (INSERM, UNIV. DE CAEN & SOC. CIVIL BIOPROJET) 15 October 1986 see claims 1-12; examples 1,45,46,58 ---	1-23
X	WO,A,93 12107 (SCHERING CORPORATION) 24 June 1993 see claims 1-20 ---	1-23
X	FARMACO, vol.47, no.11, 1992, PAVIA IT pages 1343 - 1365 F. BORDI ET AL 'Synthesis and binding assays of H3-receptor ligands' see page 1343 - page 1351 ---	1-23
X	GB,A,1 305 548 (SMITH KLINE & FRENCH) 7 February 1973 see page 1; claims 1-11; examples 1-10 ---	1-23
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 December 1994	15. 12. 94

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax (+31-70) 340-3016	Voyiazoglou, D

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Intern. nal Application No
PCT/NL 94/00206

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE,A,21 31 625 (SMITH KLINE & FRENCH) 30 December 1971 see claims 1-10	1-23

2

INTERNATIONAL SEARCH REPORT

In ational application No.
PCT/NL94/00206

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claims searched incompletely: 1-9, 11, 18-23

Please see attached sheet ./.

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/

As the drafting of the claims is not clear and concise (Art. 6, PCT) and encompasses such an enormous amount of products a complete search is not possible on economic grounds (See Art. 17(2)(a)(11),PCT). Guided by the spirit of the application and the inventive concept as disclosed in the descriptive part of the present application the search has been based on examples.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. .nal Application No
PCT/NL 94/00206

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0197840	15-10-86	FR-A-	2579596	03-10-86
		JP-A-	61267574	27-11-86
		US-A-	4707487	17-11-87
WO-A-9312107	24-06-93	AU-B-	3275893	19-07-93
		CA-A-	2126086	24-06-93
		EP-A-	0619818	19-10-94
GB-A-1305548	07-02-73	NONE		
DE-A-2131625	30-12-71	BE-A-	768474	14-12-71
		CH-A-	551409	15-07-74
		FR-A,B	2100822	24-03-72
		NL-A-	7108585	28-12-71
		US-A-	3808336	30-04-74
		US-A-	3908014	23-09-75
		GB-A-	1307539	21-02-73